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REMARKS

Claims 28, 29 and 41-43 are pending in the application. Claims 1-27 and 30-40 have been cancelled without prejudice.

First of all, Applicants wish to thank the Examiner and her supervisor for the interview and for their assistance to advance prosecution of this application.

Claim rejections - 35 U.S.C. § 102

The rejection of claims 28 and 29 under 35 U.S.C. § 102(b) for allegedly being anticipated by Andreola *et al.* is maintained. The Examiner mentioned that in the last response submitted August 14, 2006, it was argued that Andreola teaches the identification of oligonucleotides having anti-viral activity due to their sequence (sequence dependent mode of action). The Examiner further argued that, with respect to the arguments that Andreola only teaches oligonucleotides having anti-viral activity due to the sequence, it is stated on page 267 of Andreola that oligonucleotides folding into pseudoknot motif were found to bind HIV-1 RT with high affinity (column 2, first partial paragraph). In addition, Andreola teaches that the SELEX approach has also been used to identify high affinity DNA ligands against HIV-1 RT. Even though they show little structural similarity to RNA aptamers, they were able to bind to the RT and specifically inhibited the DNA polymerase activity. Thus, there is no teaching in Andreola *et al.* that the antiviral activity is limited only to particular specified sequences.

Furthermore, during the telephone interview, a point was made to the effect that Andreola *et al.* only discloses sequences targeted against RT-HIV-1, and that the antiviral activity observed by Andreola *et al.* is inherently derived from the same method as in the present application.

In order to overcome this rejection, Applicants submit that claim 28 has been amended to a method for the prophylaxis or treatment of specific viral infections not disclosed by Andreola et al. More particularly, the method as now claimed herein comprises the step of administering to a subject in need of such treatment a therapeutically effective amount of at least one pharmacologically acceptable formulation comprising at least one

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antiviral oligonucleotide having an antiviral activity, said viral infection being caused by a virus of the family selected from the group consisting of herpesviridae, poxviridae, hepadnaviridae, arenaviridae, bunyaviridae, coronaviridae, filoviridae, flaviridae, orthomyxoviridae, paramyxoviridae, rhabdoviridae and togaviridae. Support for this amendment can be found throughout the application and, more particularly, in paragraph [0083] and Examples 1-3 and 5-8, of the present description. Contrary to the teaching found in the present application and as acknowledged by the Examiner, Andreola *et al.* only teaches a specific sequence having high affinity to RNase H domain of HIV-1 RT. Nowhere is it taught or even suggested in Andreola *et al.* oligonucleotides having an antiviral activity against other viruses, such as viruses of the family now claimed in amended claim 28. Thus, since Andreola *et al.* only discloses oligonucleotides which are inhibitors of the HIV-1 RT, it is believed that the present application is new and inventive in view of the teaching of Andreola *et al.* In view of the arguments and amendment submitted hereinabove, reconsideration of the Examiner's rejections is respectfully requested.

The Examiner also maintains her rejection of claims 28 and 29 under 35 U.S.C. 102(c) as being anticipated by Peyman *et al.* The Examiner mentioned that the response submitted August 14, 2006, with respect to the fact that Peyman *et al.* only teaches that the efficacy of the tested oligonucleotides is dependent on the presence of 10 guanines extension at each extremity of the oligonucleotide, was not convincing. The Examiner alleged that this argument relates to the G-quartet structures which are not mentioned in the claims. Furthermore, the Examiner alleged that Peyman *et al.* teaches administering the same oligonucleotides as those of the claimed invention (oligonucleotides of at least 10 nucleotides in length) and teaches administering the oligonucleotides to the same patient population as the present invention. Therefore, since Peyman teaches administering the same composition to the same patient population, the method of Peyman anticipates the claimed invention. The Examiner concluded that the oligonucleotide composition of Peyman has antiviral activity acting by a sequence independent mode of action.

In order to overcome this rejection, Applicants respectfully submits that nowhere is it taught or even suggested in Peyman *et al.* that oligonucleotides have antiviral activity against multiple viruses acting by a sequence independent mode of action. Moreover, Peyman *et al.*

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is only enabled for four antisense oligonucleotides against HSV-1 in cell culture (as disclosed in column 14, lines 14-19 in Peyman). Peyman *et al.* only teaches how to stabilize and improve cell penetration by capping oligonucleotides (with the addition of a cap of guanine at their extremities). When considering the sequences disclosed by Peyman *et al.*, all of the sequences disclosed therein are antisenses. Moreover, Peyman *et al.* in column 6, lines 8-9 teaches that the effective oligonucleotides are understood to mean antisense oligonucleotides. By definition, an “antisense” is a molecule that interacts with complementary strands of nucleic acids, modifying the expression of genes. Consequently, a person skilled in the art would recognize that an antisense RNA or single-stranded antisense DNA is a molecule which is complementary to the nucleic acid sequence of a gene of interest. Thus, the mechanism of action of an antisense is sequence dependent since it must be complementary to a strand of nucleic acids in order to interact and modify the expression of the gene of interest. In addition, such person skilled in the art would come to the conclusion that SEQ ID NOs: 1-34 represent sequences that are complementary to a known gene, and thus represent possible antisense oligonucleotides. The following Table identifies the gene targeted by these antisenses:

Patent Seq ID	Sequence	Homologous to (% coverage)	Accession #
1	ACACCCAATTCTGAAAATGG	HIV-1, complete genome (100)	AF003819.3
2	AGGTCCCTGTTGGGGCGCCA	HIV-1 proviral DNA, complete genome (100)	AB289588.1
3	GTCGACACCCAATTCTGAAAATGGATAA	HIV-1, complete genome (100)	AF003819.3
4	GCTATGTCGACACCCAATTCTGA AA	HIV-1 proviral DNA, complete genome (100)	AB287367.1
5	GTCGCTGTCTCCGCTTCTTCTTCCTG	HIV-1 isolate B055AA from USA tat protein (tat) gene, partial cds (100 [bases 1-22])	AY734162.1
6	GTCTCCGCTTCTTCTTCCTGCCATAGG	HIV-1 proviral DNA, complete genome (100 [bases 10-27])	AB289588.1
7	GCGGGGCTCCATGGGGTCG	Human herpesvirus 1 complete genome (100)	X14112.1
8	CAGCTGCAACCCAGC	Homo sapiens angiotonin like 1 (AMOTL1), mRNA (100)	NM_130847.2
9	GGCTGCTGGAGCGGGGCACAC	Homo sapiens MYC gene for c-myc proto-oncogene and ORF1 (100)	X00364.2
10	AACGTTGAGGGCAT	Homo sapiens v-myc myelocytomatosis viral oncogene homolog (100)	NM_002467.3
11	GTGCCGGGTCTTCGGGC	Homo sapiens mRNA for v-myb myeloblastosis viral oncogene (100)	AJ616235.1
12	GGAGAACATCATGGTCGAAAG	Mouse c-fos oncogene (100)	V00727.1
13	CCCGAGAACATCATGGTCGAAAG	Mouse c-fos oncogene (100)	V00727.1
14	GGGGAAAGCCCGGCAAGGGG	Mouse c-fos oncogene (100)	V00727.1
15	CACCCGCCCTGGCCTCCCAC	Multiple human genomic hits (100)	
16	GGGACTCCGGCGCAGCGC	Human mRNA for precursor of epidermal growth factor receptor (100)	X00588.1

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Patent Seq ID	Sequence	Homologous to (% coverage)	Accession #
17	GGCAAACCTTCTTTCTCC	Homo sapiens epidermal growth factor receptor (100)	NM_201284.1
18	GGGAAGGAGGAGGATGAGG	Mus musculus mRNA for p53, complete cds (100)	AB020317.1
19	GGCAGTCATCCAGCTTCGGAG	Mouse mRNA for transformation associated protein p53 (100)	X00741.1
20	GCAGTAAGCATCCATATC	Felis catus integrin beta 1 (100)	NM_001048160.1
21	CCCCCACCCTTCCCCCTCTC	Homo sapiens intercellular adhesion molecule 1 (100)	BC015969.2
22	CTCCCCCACCCTTCCCCCTC	Homo sapiens intercellular adhesion molecule 1 (100)	BC015969.2
23	GCTGGGAGCCATAGCGAGG	Homo sapiens intercellular adhesion molecule 1 (100)	BC015969.2
24	ACTGCTGCCTTGTCTCAGG	Homo sapiens HES2 gene (100 [bases 2-16] and multiple genomic hits (100)	NM_019089.3
25	CAATCAATGACTTCAAGAGTTC	Homo sapiens selectin E (endothelial adhesion molecule 1) [bases 7-22] and multiple genomic hits (100)	NM_000450.1
26	GGTCCCTGTTGGCGCCA	HIV-1 proviral DNA, complete genome (100)	AB289588.1
27	GTGCCGGGGTCTTCGGG	Homo sapiens mRNA for v-myb myeloblastosis viral oncogene (100)	AJ616235.1
28	GGAGGATGCTGAGGAGG	Human herpesvirus 1 gene for DNA polymerase UL30 (100)	AB231460.1
29	GGAGGATGCTGAGG	Human herpesvirus 1 gene for DNA polymerase UL30 (100)	AB231460.1
30	CAGGAGGATGCTGAGGAGG	Human herpesvirus 1 gene for DNA polymerase UL30 (100)	AB231460.1
31	GGCTGCCATGGTCCC	Homo sapiens fibroblast growth factor 2 (100)	NM_002006.3
32	TCATGGTGTCCCTTGCAGCC	Homo sapiens procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 (100 [bases 1-15] and multiple genomic hits (100)	NM_001084.4
33	TCATGGTGTCCCTTGCAG	Homo sapiens procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 (100 [bases 1-15] and multiple genomic hits (100)	NM_001084.4
34	AAGTTCATGGTTTCGG	Homo sapiens vascular endothelial growth factor A (100)	NM_003376.4

In column 6, lines 30-31; column 8, lines 29-30; column 10, lines 35-36; column 11, lines 4-5; and column 14, lines 14-19 of Peyman *et al.*, it is clearly stated that the following oligonucleotides are examples of novel antisense effective against the following targets:

SEQ ID NOS	Target gene
35-46	HIV
47-54	HSV-1
55-56	c-Ha-ras
57-60	c-myc
61-63	c-myb
64-70	c-fos
71-72	p120
73-77	EGF receptor

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SEQ ID NOS	Target gene
78-81	p53 tumor suppressor
82-83	bFGF
84	VEGF
85-86	VLA-4
87-94	ICAM
95-98	ELAM-1
99-103	TNF-alpha
104-105	HSV-1

Consequently, SEQ ID NOS: 1-105 all represent antisense oligonucleotides which are complementary to a portion of the nucleic acid sequence of a specific gene. Thus, by its inherent properties, as well as by definition, an antisense will modify the expression of a gene by a sequence dependent mode of action. The present application teaches oligonucleotides having a sequence independent mode of action. For example, with randomer oligonucleotides, as taught in the present description, due to the nature of the preparation used to produce them, a sequence complementary mode of action cannot occur. On page 34 of the present description, it is clearly disclosed that for a randomer oligonucleotide of 40 bases in length, any particular sequence in the population would theoretically represent only $1/4^{40}$ or 8.27×10^{-25} of the total fraction. Given that 1 mole = 6.022×10^{23} molecules, and the fact that the largest synthesis is currently done on a 15 micromole scale, all possible sequences will not be present. Also, there is most probably only one copy of each sequence. Consequently, by its inherent properties, the mode of action of these oligonucleotides is sequence independent and does not require complementarity to the nucleic acid sequence of a gene.

In addition, it is clearly stated in Peyman *et al.* (column 1 and 2, under the Summary section), that:

"It has now been found that a very simple option exists for significantly improving unmodified or modified oligonucleotides with regards to their nuclease resistance and cell penetration, so that their activity is substantially improved, by extending the oligonucleotides at the 3' end and/or 5' end by from one to 10 guanines.

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Surprisingly, the novel oligonucleotide also exhibit a tendency to associate or aggregate. It is possible that they too form G quartet structures by the association of two or more oligonucleotide. Such structures would protect against exonuclease degradation and lead to an increased uptake in cell."

Thus, Peyman *et al.* discloses and claims antisenses which are complementary to a target sequence and which have a Cap of guanine(s) at its 5' and/or 3' extremity. Nowhere in the present application is it taught, claimed or required that the oligonucleotides of the present invention need to possess a Cap of guanines in order to increase its nuclease resistance and cell penetration, or that they be antisense or have sequence complementarity to a target so that their activity will be improved. Again, a person skilled in the art would recognize that Peyman *et al.* teaches antisense oligonucleotides wherein the stabilized antiviral activity depends on the presence of a Cap of guanines. Thus, the stabilization of the antisenses disclosed in Peyman is dependent on the presence of a secondary structure since, as stated in Peyman *et al.* (see column 1, lines 55-57), oligonucleotides which contain short segments of G residues are able to form intramolecular structures called G-quartets. Thus, not only is the antiviral activity dependent on the sequence, but the stabilization of the antisenses disclosed in Peyman is sequence dependent (in order to form the G-quartet structure).

In view of the arguments presented hereinabove, it is believed that the claims now on file are novel and inventive in view of the teaching of Peyman *et al.*, and thus reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

Double Patenting

Claims 28 and 29 have been provisionally rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-2 and 14-32 of co-pending Application No. 10/661,099. This rejection should now be moot in light of the Terminal Disclaimer which was filed June 8, 2006 in Application Serial No. 10/661,099, disclaiming the terminal portion of the term on an eventual patent extending beyond the term of an eventual patent granted on this application.

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Claims 28 and 29 have been provisionally rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-38 of co-pending Application No. 10/661,088. In order to overcome this rejection, Applicants respectfully submit that a terminal disclaimer is concurrently being submitted in co-pending Application No. 10/661,088.

Claims 28 and 29 have been provisionally rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-2 and 14-32 of co-pending Application No. 10/661,415. Applicants respectfully submit that a terminal disclaimer is concurrently being submitted in co-pending Application No. 10/661,099.

It is submitted, therefore, that the claims are in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 28, 29, 41, 42 and 43 at an early date is solicited.

No additional fees are believed to be necessitated by this amendment. Should this be in error, authorization is hereby given to charge Deposit Account No. 19-5113 for any underpayment or to credit any overpayment.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application can be expedited.

Respectfully,

Date: February 9, 2007

By:



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